Remarks

Reconsideration and withdrawal of the outstanding rejections are respectively requested. Claims 10-22, 47, and 56-67 are now pending in this application with claims 10-12, 18, 20 and 47 being the independent claims. Reconsideration of claims 10-22, 47, and 56-67 is respectfully requested.

I. Support for the Amendment

Support for the foregoing amendment to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendment to independent claims 10-12, 18, 20 and 47 may be found in the specification at page 10, line 25; page 11, lines 24-28; page 12, lines 1-4; page 15, lines 21-27; and page 26, lines 6-14. Applicants respectfully request that the Examiner enter this amendment after final rejection. Claim 10 was amended merely to delete "detection" and to recite "only." The remaining claims were also amended to recite "only." Therefore, this amendment does not add new matter or require any additional consideration or searching. Entry is thus appropriate and earnestly solicited.

II. Objection to the Claims

The Examiner objected to claims 10-22 and 47 because the claims include limitations from non-elected claims. Applicants respectfully disagree. Applicants elected Group II in response to the Restriction Requirement dated March 20, 2001. Group II includes claims 10-22, 47 and is drawn to a method of detection or amplification. The remaining groups are

directed to a nucleic acid composition (claims 1-9, 23-30 and 41-46; Group I); methods of making a nucleic acid composition (claims 31-32 and 55; Group III); and methods of mutation detection (claims 33-40 and 48-54; Group IV). The pending claims are directed to a method of detection or amplification and are distinct from the non-elected claims, as set forth in the Restriction Requirement. Applicants have amended claims which would not cause claims to be in non-elected group. Therefore, reconsideration and withdrawal of this objection are respectfully requested.

III. The Rejection Under 35 U.S.C. § 102(b) Over Heller is Traversed

In the Office Action at pages 2-3, the Examiner has rejected claims 10-16, 18, 20-22, 47, 56-58, 60-62 and 65-67 under 35 U.S.C. § 102(b) as being anticipated by Heller, U.S. Patent No. 5,565,322 (Doc. A on the Notice of References Cited by Examiner, accompanying paper no. 7; hereinafter "the '322 patent"). Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single enabling prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). This requirement is not met by the disclosure of the '322 patent, which therefore cannot anticipate the invention as claimed.

The '322 patent discloses polynucleotides that contain fluorescent or non-fluorescent

labels that assemble as organized structures onto a target DNA sequence to produce a structure capable of extended energy transfer upon hybridization. Claim 10 is drawn to methods for the quantitation of one or more target nucleic acid molecules in a sample. The '322 patent does not disclose methods for the quantitation of nucleic acid molecules in a sample. Therefore, the rejection to amended claim 10 must be withdrawn.

Furthermore, claims 11-16, 18, 20-22, 47, 56-58, 60-62 and 65-67 are drawn to methods of detecting and quantifying amplified, synthesized or PCR products. The '322 patent does not disclose, suggest or otherwise contemplate methods of detecting or quantifying amplified, synthesized or PCR products. Therefore, the '322 patent does not disclose Applicants' claimed invention.

Hence, the '322 patent fails to expressly or inherently disclose every element of the invention as claimed, and therefore cannot form the basis of a proper rejection under 35 U.S.C. § 102(b). Reconsideration and withdrawal of the rejection are therefore respectfully requested.

IV. The Rejection Under 35 U.S.C. § 103(a) Over Nazarenko In View of Weimer is Traversed

In the Office Action at pages 4-6, the Examiner has rejected claims 10-22, 47 and 56-67 under 35 U.S.C. § 103(a) as being unpatentable over Nazarenko *et al.*, *Nucl. Acids Res. 25(12)*:2516-2521 (1997) (Doc. AR11 on the Information Disclosure Statement, filed on January 12, 2001; hereinafter "Nazarenko") in view of Weimer *et al.*, U.S. Patent No. 6,248,526 (Doc. AD6 on the Third Supplemental Information Disclosure Statement filed on July 18, 2001; hereinafter "the '526 patent"). Applicants respectfully traverse this rejection.

Applicants respectfully believe the remarks made in the Amendment and Reply

Under 37 C.F.R. § 1.111, filed November 28, 2001, were sufficient to overcome and traverse each element of the rejection in the Office Action. Therefore, Applicants reiterate and incorporate by reference herein their previous remarks. Applicants also wish to make the following additional remarks concerning this rejection.

As previously stated, Nazarenko does not disclose, suggest or otherwise contemplate the methods of the claimed invention. Nazarenko teaches the use of labeled oligonucleotides having a label on the 5'-end. Nazarenko does not disclose, suggest, or otherwise contemplate oligonucleotides having only internal labels. Therefore, Nazarenko is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

The '526 patent does not cure these deficiencies of Nazarenko, since the methods disclosed in the '526 patent are significantly different from those of the present invention. The Examiner states that "the '526 patent expressly states regarding the TAMRA label that 'In another preferred embodiment, a label or label system is attached to the primer at or ***near*** its 3' end and has an interactive label (column 2, lines 43-45 (emphasis mine))." Office Action, page 9. Applicants respectfully submit that the Examiner has taken this statement out of context. The '526 patent states that:

> [a]t least one, and preferably at least the last two to five, or more, nucleotide at the 3' end of the primer are deliberately mismatched to the DNA or nucleic acid sequence to be amplified. The label or part of a label system is attached to the 3'-terminal mismatched portion, preferably to the 3' end nucleotide. . . . Under the influence of the polymerase employed for the amplification, which possesses proof-reading or nuclease properties equivalent to such, the unpaired bases of the labeled primer, together with the label, e.g., the reporter dye molecule or quencher molecule, are released by the 3'→5' nucleolytic activity of the polymerase before the actual elongation reaction takes place. In the

> process, the quencher is removed from spatial proximity to the reporter dye.

The '526 patent, column 2, lines 46-64. Therefore, one of ordinary skill in the art would not combine the teachings of Nazarenko together with the '526 patent. The methods described in Nazarenko are entirely different than the methods described in the '526 patent. Moreover, even if one were to combine Nazarenko with the '526 patent, they would not obtain Applicants' invention. The Examiner has not established why one of ordinary skill in the art would ignore the teachings of the '526 patent regarding the use of mismatched bases and the use of a polymerase having a 3'→5' exonuclease activity to release a reporter dye or quencher molecule.

Therefore, Nazarenko and the '526 patent, alone or in combination, do not disclose or suggest methods of the claimed invention. Accordingly, reconsideration and withdrawal are respectfully requested.

V. The Rejection Under 35 U.S.C. § 103(a) Over Heller In View of Nazarenko is Traversed

In the Office Action at pages 6-9, the Examiner has rejected claims 10-22, 47 and 56-67 under 35 U.S.C. § 103(a) as being unpatentable over the '322 patent in view of Nazarenko. Applicants respectfully traverse this rejection.

As previously stated, the '322 patent does not disclose, suggest or otherwise contemplate the claimed invention. Notably, the '322 patent does not disclose methods for the quantitation of nucleic acid molecules in a sample, nor does it disclose methods of detecting or quantifying amplified, synthesized or PCR products. Therefore, the '322 patent is seriously deficient as a primary reference upon which to base a *prima facie* case of

obviousness.

Nazarenko does not cure these deficiencies of the '322 patent, since Nazarenko teaches primers labeled at the 5'-terminus. Therefore, one of ordinary skill in the art would not obtain Applicants' claimed invention if they were to combine the '322 patent with Nazarenko.

The Examiner states that:

> [i]t would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Heller detection method using PCR with a hairpin primer as taught in the Nazarenko method since Heller states "A multiple donor system comprised of such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications". Thus, an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce the background to as low a level as possible.

Office Action, pages 7-8 (citations omitted). Applicants respectfully disagree with the Examiner. It is well known to one of ordinary skill in the art that the use of a quencher molecule with a fluorescence label results in lower fluorescence if the moieties are within close distance to one another. This accounts for the lower background levels in the '322 patent, if a quencher molecule is used with a fluorescence label. However, the Examiner does not explain why one of ordinary skill in the art would combine the detection method of the '322 patent and its use of linear primers with the quantitation method of Nazarenko and its use of hairpin primers. The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir.

1990).

Contrary to the Examiner's assertion, Nazarenko does not provide motivation to combine its teachings with the '322 patent. In particular, Nazarenko states that "[t]he main advantage of this method is the generation of the fluorescent signal by the product itself, rather than by the hybridized probe, as in previous methods. This keeps background low and allows real-time quantification of the amplified DNA over an extremely wide dynamic range." Nazarenko, page 2521, col. 1, lines 7-9 (citations omitted). In contrast, the '322 patent teaches detection of hybridized polynucleotides. Therefore, there is no reason why one of ordinary skill in the art would combine such different methods.

The Examiner further states that "[r]outine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way." Office Action, page 9. Applicants respectfully disagree with the Examiner. Contrary to the Examiner's assertion, it is not mere routine optimization to determine the specific positioning of the label. Applicants have shown that "[t]o achieve a quenching effect the labeled base should be within 10 nucleotide distance from the 3'-end, preferably within 6 nucleotides and most preferably within 1-4 nucleotides." Applicants' specification, page 52, lines 23-26. Applicants also refer to Figure 2 which shows that internally labeled primers showed an increase in fluorescence when converting from single-stranded to double-stranded forms. Consequently, the present invention is a significant advance in the art and not the result of routine optimization.

Therefore, the '322 patent and Nazarenko, alone or in combination, do not disclose or suggest the claimed invention. Accordingly, reconsideration and withdrawal are respectfully requested.

VI. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 10-12, 18, 20 and 47 are amended as follows:

10. (Twice amended) A method for the quantification [or detection] of one or more target nucleic acid molecules in a sample comprising hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be [detected or] quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule, and [detecting the presence or absence and/or] quantifying the amount of said one or more target nucleic acid molecules.

11. (Twice amended) A method for the quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid synthesis comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule;

incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to all or a portion of said one or more templates, said one or more synthesized nucleic acid molecules comprising said one or more oligonucleotides; and

detecting the presence or absence or quantifying the amount of said one or more synthesized nucleic acid molecules by measuring said one or more detectable labels.

12. (Twice amended) A method for quantitation or detection of one or more nucleic acid molecules in a sample during nucleic acid amplification comprising:

mixing one or more nucleic acid templates with one or more oligonucleotides under conditions sufficient to amplify one or more nucleic acid molecules complementary to all or a portion of said one or more templates, said one or more amplified nucleic acid molecules comprising said one or more oligonucleotides, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule; and

detecting the presence or absence or quantifying the amount of said one or more nucleic acid molecules by measuring the detectable labels of said oligonucleotides.

18. (Twice amended) A method for amplifying a double stranded nucleic acid molecule, comprising:

providing a first and second primer, wherein said first primer is complementary to a sequence within or at or near the 3´-termini of the first strand of said nucleic molecule and said second primer is complementary to a sequence within or at or near the 3´-termini of the second strand of said nucleic acid molecule;

hybridizing said first primer to said first strand and said second primer to said second strand in the presence of one or more polymerases, under conditions such that a third nucleic acid molecule complementary to all or a portion of said first strand and a fourth nucleic acid molecule complementary to all or a portion said second strand are synthesized;

denaturing said first and third strands, and said second and fourth strands; and

repeating the above steps one or more times, wherein one or more of the primers comprise a detectable label located only internally.

20. (Twice amended) A method for the quantification or detection of nucleic acid molecules comprising:

mixing one or more labeled oligonucleotides with one or more nucleic acid molecules to be detected or quantitated, wherein said one or more oligonucleotides comprise one or more detectable labels located only internally; and

detecting or measuring an increase in fluorescence associated with said one or more oligonucleotides hybridizing to said one or more nucleic acid molecules.

47. (Twice amended) A method for detecting a target nucleic acid sequence, comprising:

contacting a sample containing a mixture of nucleic acid molecules with at least one oligonucleotide capable of hybridizing with a target nucleic acid molecule and comprising a detectable moiety located only internally, wherein the detectable moiety undergoes a change in one or more observable properties upon hybridization to the target nucleic acid molecule; and

observing the observable property, wherein a change in the observable property indicates the presence of the target nucleic acid sequence.